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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/030,658	01/11/2002	Ken-Ichi Yamamura	4456-0101P	4644

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EXAMINER	
QIAN, CELINE X	

ART UNIT	PAPER NUMBER
1636	

DATE MAILED: 05/05/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/030,658	YAMAMURA ET AL.	
	Examiner	Art Unit	
	Celine X. Qian Ph.D.	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 March 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-12,19 and 20* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-6,9-12,19 and 20* is/are rejected.

7)☒ Claim(s) *7 and 8* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *11 January 2002* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-12, 19 and 20 are pending in the specification.

This Office Action is in response to the Amendment filed on 3/22/06.

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 3/22/06 has been entered.

Response to Amendment

The rejection of claims 9 and 10 under 35 U.S.C. 102 (e) is moot in view of the new ground of rejection discussed below.

The rejection of claims 1-6, 11 and 12 under 35 U.S.C. 103 (a) is moot in view of the new ground of rejection discussed below.

The rejection of 19 under 35 U.S.C. 112 1st paragraph is maintained for same reason as set forth of the record mailed on 9/22/05 and further discussed below.

New Grounds of Rejection

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1 and 4 are rejected under 35 U.S.C. 102(b) as being anticipated by Elledge et al (US 5,851,808).

The claims are drawn to a trap vector that comprises a wild type loxP and a mutant loxP, wherein the mutant loxP has mutation either in the first inverted repeat sequence or the second inverted repeat sequence.

Elledge et al. disclose a vector comprises a wild type loxP and a mutant loxP, wherein the mutant loxP has mutation either in the first inverted repeat sequence or the second inverted repeat sequence (see Figure 12 and 13, and col. 29 through col. 30, bridging paragraph). Therefore, Elledge et al. disclose the instantly claimed invention.

Claims 9 and 10 are rejected under 35 U.S.C. 102(b) as being anticipated by Albert et al (see IDS).

The claims are drawn to a vector generated from recombination between a first trap vector comprising a loxP and a mutant loxP and a second vector comprising a loxP and a mutant loxP. Claim 10 is further drawn to such a vector wherein it does not recombine with another loxP. The claims are product by process claims, which read on the product. The process in which the product was made does not impart a structural difference to the product has no patentable weight. As such, the claims are drawn to a vector comprising two loxP sites that cannot be recombined.

Albert et al. disclose a vector comprising two loxP sites that cannot be recombined (see page 650, Figure 2b, Luc+). Applicants indicate that the claimed invention comprises mutant loxP having mutation in inverted repeat sequence rather than the spacer region. The mutant loxP

disclosed by Albert et al. comprises mutation in inverted repeat sequence (see page 651, Figure 3, for example, lox71 and lox66). Therefore, Albert et al. disclosed the instantly claimed invention.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 2, 3, 5 and 6 are rejected under 35 U.S.C. 103(a) as being unpatentable over Elledge et al., in view of Albert et al.

The teaching of Elledge et al. is discussed above. Elledge et al. further teach mutant loxP2 or loxP3 that comprises mutation in the inverted repeat sequence of loxP. Elledge et al. further teach that other mutated loxP site can also be used (see col. 31, lines 35-39). However, Elledge et al. do not teach a vector comprises wild type loxP and lox71 or lox66.

The teaching of Albert et al. is discussed above. Albert et al. also teach that lox71 and lox66 recombines more efficiently in the forward reaction than wild type loxP (see Table 1).

It would have been obvious to one of ordinary skill in the art that lox71 and lox66 can be used instead of loxP2 or loxP3 in the vector taught by Elledge et al. One of ordinary skill in the art would have been motivated to do so because the increased recombinant activity of said mutant sites. The level of skill in the art is high. Absent evidence from the contrary, one of ordinary skilled in the art would have reasonable expectation to replace the mutant loxP sites in

the vector taught by Elledge with lox71 and lox66 taught by Albert et al. Therefore, the claimed invention would have been *prima facie* obvious at the time the invention was made.

Claims 11, 12, 19 and 20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Leboulch et al., in view of Araki et al (1997, Nucleic Acid Research, Vol.25, No.4, pages 868-872) and Albert et al.

Leboulch et al. disclose a vector comprising two loxP sites that cannot be recombined (see claim 1, col. 5, 3rd and 4th paragraph). Leboulch et al. also teach that one of the embodiments of the two loxP sequence can be a loxP1 and a mutant form of loxP (see col. 5, 2nd and 3rd paragraph). Leboulch et al. further teach that the acceptor vector is preferably integrated into genome wherein exchange of genetic elements occurs when the donor vector is introduced (col. 3, last paragraph through col. 4, 4th paragraph). However, Leboulch et al. do not teach the mutant loxP is lox71 or lox66.

Arakai et al. teach site directed DNA integration has been achieved by using a pair of mutant loxP sites, lox71 and lox66, in mouse ES cells (see page 870, bridging paragraph). Arakai et al. also teach that the integration frequency with the mutant sites is much higher than wild type loxP sites or between the wild type and the mutant sites (see Table 1).

The teaching of Albert et al. is discussed above.

It would have been obvious to one of ordinary skill in the art to use the combination of wild type loxP and lox71 or wild type loxP and lox66 in the donor or acceptor vector taught by Leboulch et al. based on the combined teaching of Leboulch et al., Arakai et al and Albert et al. Since Leboulch et al. teach a system of site specific recombination of transgene that comprises donor and acceptor vectors comprising a set of loxP sites that do not recombine intramolecularly

but intermolecularly, and Arakai et al. teach that loxP and lox71 or lox66 does not recombine effectively in mouse ES cells, one of ordinary skill in the art would have been motivated to use the combination of wild type loxP and lox71 or lox66 in such system to promote transgene integration at desired site. Further, Albert et al. teach that the forward reaction between lox71 and lox66 is more efficient than wild type loxP, thus such pair of mutant loxP sites are preferred in the recombinant event taught by Leboulch et al. The level of skill in the art of molecular cloning is high. Since the sequence of wild type and mutant loxP such as lox66 and lox71 is known, one of ordinary skill in the art would have reasonable expectation of success to make the claimed vector comprising two loxP sites, one being the wild type and the other being a mutant form as claimed. Therefore, the claimed invention would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Claim Objections

Claims 7 and 8 are objected to for containing non-elected subject matter. Applicant elected g) lox71-integrated SA-M-loxP-pA-lox2272-PV-lox511 for examination in the response filed on 10/7/04.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 19 rejected under 35 U.S.C. 112, first paragraph, as based on a disclosure which is not enabling. The critical components of the trap vector, such as the SA, IRES and marker

gene, critical or essential to the practice of the invention, but not included in the claim(s) is not enabled by the disclosure. See *In re Mayhew*, 527 F.2d 1229, 188 USPQ 356 (CCPA 1976).

The claims is drawn to a method of gene trapping, said method comprising introducing into ES cells: a first trap vector comprising a wild type and a mutant loxP sequence, and a marker gene, wherein the mutant loxP comprises a mutation in the inverted repeat sequence 1 of the wild type loxP sequence; a second trap vector comprising a wild type and a mutant loxP sequence, wherein the mutant loxP comprises a mutation in the inverted repeat sequence 2 of the wild type loxP sequence; culturing the embryonic stem cells; and selecting cells which exhibit a pattern of single copy integration of the trap vector, and isolating the trapped gene.

According to the disclosure of the specification, critical components such as SA, IRES is also required for the practice of the "gene trapping method." The claim is very broad because it is directed to use vector that comprises wild type and mutant loxP, and a marker gene. The art does not teach a gene trapping method using vectors that comprises loxP sites and marker gene only. In fact, the successful trapping of endogenous and screening such gene relies on those critical elements that are not recited in the claims. Therefore, the claimed method is not enabled.

In response to Applicants' assertion that claim 7 has been allowed and recites a trap vector comprising a marker gene, it is reminded that only g) part of claim 7 is allowable. Thus, the method of using trapping vector comprises only loxP sites and a marker gene is not enabled by the instant specification.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Celine X. Qian Ph.D. whose telephone number is 571-272-0777. The examiner can normally be reached on 9:30-6:00 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel Ph.D. can be reached on 571-272-0781. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Celine X Qian Ph.D.
Examiner
Art Unit 1636

CELINE QIAN, PH.D.
PRIMARY EXAMINER